REMARKS

Applicants have the following comments in response to the Office Action of April 21, 2005.

I. Claim Amendments – Reference to Disclosure

As explained in depth below, while Applicants respectfully traverse the rejections in the April 21, 2005 Office Action, in order to advance the prosecution of this application, independent Claims 1, 31, 68 and 85 have been amended to bring them into better conformance with the disclosure in the present application.[1] Therefore, the claimed invention is more explicitly directed to methods of photodynamic treatment wherein topically-applicable photodynamic medicaments are photoactivated within approximately 30 minutes following application. Examples in support of such claimed methods are found throughout the specification, as discussed *infra*.

Photodynamic therapy (PDT) consists of the use of pharmaceutical compositions or medicaments (i.e., photosensitizers) that are photoactivated under specific conditions. Accordingly, such compositions, in order to function, must include both the photosensitizer itself and the activating light. Ideal photosensitizers should have no therapeutic effect until such application of light, which occurs subsequent to photosensitizer administration. Nonetheless, while it is an objective in PDT to provide photosensitizers that are inactive in the absence of

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[1]In addition, Claims 11, 17 and 80 have been amended to eliminate certain irregularities in the claim language, and Claims 6-10, 12, 15, 18, 22, 65-66, 73-76, 78 and 81 have been canceled without prejudice or disclaimer.

photoactivation, PDT has been plagued by a number of shortcomings, including poor targeting and non-specific photosensitivity in the absence of intentional photoactivation.

Applicants believe that these shortcomings are related, in large measure, to poor agent targeting (i.e., specificity of the photosensitizer for diseased tissue), poor agent formulation and delivery, and improper selection of activating wavelength. These shortcomings are well known in the field, as indicated by the following passage from Williams et al. (US 5, 576,013):

> "The topical sensitizing agent is applied to the tissues containing the target vessels several times a day for 1-14 days. Following the last application, *no sensitizing agent is applied for a period of 1-7 days to allow removal of sensitizing agent from adjacent tissues* while high concentrations are maintained in the tissues containing the target vessels." (col. 3, lines 61-66, emphasis added)

Thus, Williams teaches that it is necessary to provide repeated application of a "sensitizing agent" to target tissue and then allow a lengthy clearance period (i.e., a latency period of from 1 to 7 days following application) in order to overcome the effects of poor agent targeting, particularly in healthy adjacent tissue.

These teachings in Williams concerning agent application and activation are in sharp contrast to Applicants' discovery, as illustrated by the following passage from the specification of the present application, that:

> "For treatment of superficial diseased tissue, the wavelength of the light is preferably chosen so as to *allow optical penetration into the diseased tissue but to minimize further optical penetration beyond the diseased tissue into underlying healthy tissue.* For example, visible light in the spectral region between 400-600 nm may be used to afford shallow penetration depths on the order of several millimeters or less. Use of such light affords efficacy in agent activation in superficial diseased tissues while simultaneously minimizing potential for deleterious photosensitization of underlying tissue." (p. 11, lines 18-24, emphasis added)

This passage illustrates that through proper selection of activating wavelength the extent of photosensitizer activation can be controlled, thereby minimizing undesirable effects in surrounding tissue. Applicants have further discovered that the lengthy delays due to clearance of excess agent can be avoided through directed photosensitizer application, as illustrated by the following passage from the present application:

> "In a further preferred embodiment, the *PDT agent is applied directly to the diseased tissue*. Employment of direct topical application provides a number of advantages. In particular, it affords *improved targeting* of the agent specifically to the diseased tissue, *reduces the required latency period* between agent administration and light activation and thereby *shortens the treatment cycle*, substantially *eliminates the potential for systemic photosensitization*, reduces agent consumption, and reduces the overall potential for side effects from exposure to the agent. Preferably, the agent is applied as a topical spray or wash. After a brief accumulation period (generally not to exceed 30 minutes), the excess agent is removed from the tissue surface by flushing with liquid, such as with water or saline. Following this flushing, it is preferred that the residual agent associated with the diseased tissue be activated by illumination of the diseased site with visible light between 400 nm and 600 nm." (p. 14, lines 4-15, emphasis added)

Thus, these passages teach novel methods of the present application that avoid the shortcomings of prior teachings, such as those in Williams, by exhibiting (a) improved specificity for diseased tissue combined with (b) substantially reduced latency period between agent application and activation. In contrast, prior processes, such as that exemplified in Williams, require lengthy latency periods of a day or more between sensitizer application and activation.

Therefore, in accordance with the disclosure in the present application, such as the examples given above, Applicants have amended independent Claims 1, 31, 68 and 85 to include the feature that the steps of purging and activating the PDT agent are performed within approximately 30 minutes of the step of applying the agent (Claim 1) and that the step of light application is

performed within approximately 30 minutes of the step of PDT agent application (Claims 31, 68 and 85). The presently claimed methods overcome the shortcomings of prior processes, allowing the use of latency periods as brief as approximately 30 minutes. Such improvement is highly relevant as it may eliminate the need for dividing disease diagnosis and/or treatment into multiple invasive procedures staged over a period of several hours or days, as noted for example by Applicants on p. 12, lines 14-18, of the present application.

For at least the above-stated reasons, Applicants believe that such amendments clarify the claimed methods of treatment of diseased tissue and that the amendments to the claims are supported by the application as filed. Therefore, it is respectfully requested that these amendments be entered and considered at this time.

Applicants will now address each of the Examiner's specific rejections in the order in which they appear in the Office Action.

II. Claim Rejections – 35 USC §102

A. Williams

In the Office Action, the Examiner rejects Claims 1-4, 6-7, 10-18, 20-22, 29-31, 35-38, 65-66, 68-69, 71-74, 77-81 and 83-86 under 35 U.S.C. §102(b) as being anticipated by Williams et al. (US 5,576,013). This rejection is respectfully traversed.

More specifically, the Examiner alleges that Williams "discloses a method for treatment of disease, including vessels of the circulatory system, said method comprising the steps of: applying Rose Bengal and a chelator to diseased tissue to form a treatment zone... and applying light at 550 nm to said treatment zone to activate agent associated with said tissue, wherein said light penetrates said treatment zone while minimizing activation of said agent outside said

treatment zone." Even if this is true (which Applicants do not admit), as explained below, Williams fails to disclose or suggest the methods of amended independent Claims 1, 31, 68 and 85 of the present application.

First, as described *supra*, Williams does not disclose or suggest the method of amended independent Claims 1, 31, 68 and 85, wherein the steps of PDT agent application and activation by light application are performed within a period of approximately 30 minutes. Instead, the method in Williams requires repeated application of sensitizer agent over a period of 1-14 days, followed by a latency period of 1-7 days where no agent is applied, before activation can occur. See Williams, col. 3, lines 61-66.

Second, Williams does not disclose or suggest the claimed photodynamic method of the present application since the use of the terms "photosensitizers" and "photodynamic therapy" in Williams is technically incorrect, inconsistent with the teachings and definitions of the present application, and inconsistent with standard usage of these terms by those of ordinary skill in the art. Instead, Williams describes and is directed to a therapeutic process that is completely different from photodynamic therapy, as conventionally defined in the field and in the present application, and as a result, one skilled in the art would not arrive at the claimed invention upon reading this reference.

More specifically, Williams describes a therapeutic method based on dye-mediated photocoagulation (also referred to as *photothrombosis*) that is purported to be useful for treatment of vascular and neoplastic lesions. Such photocoagulation methods are based on a *photothermal* process (intense heating of blood and blood vessels upon application of intense laser energy). Although Williams states that this is a form of photodynamic therapy (PDT), such description is *completely contrary to conventional definitions of PDT*, such as those offered

by Fisher et al.[2] or how the term is defined in the present application. Specifically, PDT, as conventionally defined by those in the field (including for example Fisher et al. and Applicants in the present application), involves non-thermal, photochemical activation of photosensitizer agents.

Williams' *photothrombosis* method involves formation of a blood clot (i.e., coagulation of blood) within a blood vessel in response to application of intense optical illumination. Photocoagulation and photothrombosis, as described in Williams, comprise *thermal effects* resulting from intense illumination of tissue with light (i.e., they are photothermal processes). Neither process is in any way related to producing a *cytotoxic reaction to light*, as is required in PDT and is completely different than the method of the claims of the present application.

That Williams is not describing cytotoxic reactions to light (i.e., photodynamic therapy) is clear from the summary of invention in the reference:

> "Rather than seek to induce DNA-level changes in the target tissue, the present invention is directed to treating the blood-supplying vascular tissue to induce photothrombosis. Once the *blood supply is blocked*, the target lesion involutes and dies." (col. 3, lines 35-39 in Williams, emphasis added)

Williams disclaims any toxic mechanism that damages cells, and instead teaches that the physical mechanism described therein utilizes occlusion of the vascular system in response to intense illumination. This photothermal therapy results in blockage of blood supply to target tissues, starving, rather than poisoning, such tissues. This is not photodynamic therapy, regardless of the nomenclature utilized in Williams. Since Williams fails to attribute any

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[2] See the discussion entitled "Photochemistry and Photobiology, Type I and Type II Photochemistry" on p. 6, in Fisher et al., "Clinical and Preclinical Photodynamic Therapy," Lasers Surg. Med. 17 (1995) 2-31, (a copy is included in the IDS filed herewith) which describes the photochemical mechanism underlying PDT. Such mechanism is completely unrelated to what is described in Williams.

phototoxic effect to what is described therein, and instead teaches away from any such phototoxic effect, the disclosure in the reference would not lead one skilled in the art to photodynamic therapy.

Applicants' claimed methods are clearly directed to photodynamic therapy and not photocoagulation, as taught in Williams. The difference is clear from the teachings in the present application, such as the following:

> "The present invention is directed to a method and apparatus for topical treatment of diseased tissue, including topical or systemic *application of a PDT agent to diseased tissue*, followed by topical application of light. In general, the method involves the steps of applying a PDT agent to diseased tissue to form a treatment zone; purging excess agent; and applying light to the treatment zone to activate agent associated with the diseased tissue." (p. 8, lines 2-6, emphasis added)

This passage makes it clear that a photodynamic (i.e., PDT) agent is used to effect the desired therapeutic outcome. This key feature is reinforced by the following:

> "Preferably Rose Bengal is used as the PDT or photosensitizing agent as it is inexpensive, non-toxic, has a proven safety record in human use, has significant intrinsic lipophilic properties, exhibits both type-I and type-II PDT response and therefore can be activated by type-I, oxygen-independent mechanism and is *strongly phototoxic upon activation with light* between 500 nm and 600 nm." (p. 12, lines 20-24, emphasis added)

Thus, in conformance with standard nomenclature and the teachings in the present application, Applicants' claimed method is directed to photodynamic therapy, based on phototoxic effect of a photosensitizer. This is not the same method as the photothermal method disclosed in Williams.

Hence, Williams' disclosure is fundamentally contrary to the claimed method of the present application. Williams describes dye-mediated photocoagulation, whereas Applicants have described

and claim a photodynamic method. These are *fundamentally distinct* methods, and as such Williams cannot, taken alone or in combination with other teachings, anticipate nor render obvious the claimed invention.

For at least the above-stated reasons, Williams fails to disclose or suggest the methods of amended independent Claims 1, 31, 68 and 85 of the present application. Accordingly, these independent claims and those claims dependent thereon are patentable over the cited reference. Therefore, it is respectfully requested that this rejection be withdrawn.

B. Kolobanov

The Examiner also rejects Claims 1-4, 6-18, 20-22, 29-31, 35-38, 65-66, 68-69, 71-74, 77-81 and 83-86 under 35 U.S.C. §102(b) as being anticipated by Kolobanov et al. (US 4,973,848). This rejection is also respectfully traversed.

More specifically, the Examiner alleges that Kolobanov "discloses a method for treatment of diseased tissue, said method comprising the steps of: applying Rose Bengal ... to diseased tissue [to] form a treatment zone; and applying light at 550 nm to said treatment zone to activate agent associated with said tissue...." Even if this is true (which Applicants do not admit), as explained below, Kolobanov fails to disclose or suggest the methods of amended independent Claims 1, 31, 68 and 85 of the present application.

First, Kolobanov describes a special dual laser beam apparatus for medical treatment, consisting of a diagnostic beam ("probe or analyzing laser beam") and a therapeutic beam ("treating laser beam"), as evidenced by the following:

> "The invention described herein relates to an apparatus for the automatic adjustment of power and properties the *treating laser beam* in accordance with information obtained by means of a

> *probe or analyzing laser beam.* (Fully automated scanning is an optional feature of the invention, appropriate for some applications, but not required for those cases in which the surgeon desires to maintain manual control.) As such, it will have obvious applications to those areas of medicine and surgery described above, and others which will be obvious to practitioners having ordinary skills in those fields." (col. 3, lines 28-39, emphasis added)

Kolobanov states that a major use for this unusual device is photodynamic therapy:

> "...a major impetus for the development of this invention is for the photodynamic treatment of cancer. Such photodynamic therapy ("PDT") procedures will be the focus of our discussion and supply the primary examples for the uses of the invention described herein." (col. 3, lines 39-44)

Kolobanov continues this discussion by stating that PDT is predicated on *systemic delivery* of a photosensitizer:

> "PDT is based upon the existence of certain chemicals which are selectively retained (or conceivably, selectively absorbed) by cancer cells. It is also known that some of these selectively-retained chemicals cause destruction of the cells in which they reside when exposed to light of sufficient intensity and having the appropriate wavelength...
>
> "The leading photochemical cancer treatment at this time involves the *injection into the patient* of a hematoporphyrin derivative ("HpD"). *This drug permeates the tissues of the patient*, but *typically dissipates from normal cells in 24-48 hours*. HpD is typically retained for a longer time by cancer cells. When exposed to light of sufficient intensity and at the appropriate wavelength, HpD undergoes a chemical reaction leading to the destruction of the cell in which it resides. Thus, *appropriate timing of the exposure of the patient to light following the administration of HpD leads to selective destruction of those cancer cells exposed to said light*." (col. 3, lines 47-67, emphasis added)

Thus, Kolobanov teaches that (a) photosensitizers are applied systemically; (b) a latency period of 24-48 hours is needed to allow excess photosensitizer to dissipate from normal cells (presumably to avoid unwanted damage to such normal cells); and (c) that activating light must be applied at an appropriate time to achieve the selective treatment.

In contrast, as discussed above, the methods of the amended independent claims of the present application do not have such a latency period but instead require that the steps of purging and activating the PDT agent are performed within approximately 30 minutes of the step of applying the agent (Claim 1) and that the step of light application is performed within approximately 30 minutes of the step of PDT agent application (Claims 31, 68 and 85). As such claimed features are not disclosed or suggested by Kolobanov, Kolobanov does not disclose or suggest the method of amended Claims 1, 31, 68 and 85 of the present application.

Further, Kolobanov reiterates the need to abide by a specific latency period in the following passage, and further defines the role of the claimed dual-beam apparatus:

> "...it is necessary to exercise care in the exposure of the patient to light following HpD administration. Overexposure of the patient can lead to the unwanted death of normal cells (presumably containing trace amounts of HpD at the time of treatment with light). Underexposure will lead to incomplete destruction of the patients cancer cells, obviously leading to a recurrence of the disease. Thus, surgeons would very much like to be able to monitor the dosage delivered to each point of the affected region and, at the same time, monitor the concentration of photosensitizing chemical (typically, HpD)." (col. 4, lines 4-15)

Thus, the apparatus of Kolobanov is intended to facilitate precise delivery of light to tissue in order to avoid overexposure or underexposure of this activating energy while simultaneously monitoring the concentration of photosensitizer. This apparatus is subsequently summarized in the following passage from the reference:

> "The present invention discloses an apparatus in which two laser beams are concurrently scanned across a region to be treated. A first 'analysis' beam is used to excite characteristic light emission or reflection from the surface, which light is detected at a location remote from said surface. Said detected light is analyzed to determine the properties of the small portion of the surface under illumination at that instant by the analysis beam. A

> second 'treatment' beam is scanned concurrently with said analysis beam. The properties of the surface at each small region (as determined by the analysis beam) are used to adjust the power and other properties of said treatment beam such that each small region of the surface receives optimal processing by said treatment beam." (col. 8, line 60 to col. 9, line 61)

In contrast to these complicated teachings in Kolobanov, which are predicated on solving certain problems resulting from systemic administration of a photosensitizer, the method of the claimed invention is free of such complexity and hazard. Instead, the claimed invention is based on topical application of photosensitizer to diseased tissue (not systemic application, as is the case in Kolobanov) and use of a single light source offering controlled penetration into tissue (and hence intrinsic safety). Moreover, whereas Kolobanov requires a lengthy latency period of up to several days or more between agent application and photoactivation (see col. 3, lines 47-67), the claimed invention utilizes a latency period of approximately 30 minutes.

Thus, the complicated method in Kolobanov is distinctly different from the methods of the claims of the present application, in that Kolobanov utilizes systemic delivery of photosensitizer whereas the claimed methods utilize topical delivery; Kolobanov requires a latency period of several days or more whereas the claimed methods utilize a latency period of approximately 30 minutes; and Kolobanov requires a highly complicated apparatus capable of precisely scanning two laser beams whereas Applicants' method is free of such complexity.

For at least the above-stated reasons, Kolobanov fails to disclose or suggest the methods of amended independent Claims 1, 31, 68 and 85 of the present application. Accordingly, these independent claims and those claims dependent thereon are patentable over the cited reference. Therefore, it is respectfully requested that this rejection be withdrawn.

III. Claim Rejections – 35 USC §103

The Examiner also rejects Claims 23-28, 34 and 82 under 35 U.S.C. §103(a) as being unpatentable over Williams in view of "the admission of the present specification".[3] This rejection is also respectfully traversed.

Initially, it is noted that each of these claims is a dependent claim. Therefore, for at least the reasons discussed above for the independent claims, each of these claims is patentable over the cited references, and accordingly, it is requested that this rejection be withdrawn.

Further, as a basis for this rejection, the Examiner alleges that it would be obvious to combine the teachings of Williams with known balloon or catheter technologies to arrive at the subject claims. However, as discussed *supra*, Williams' method is distinctly different from the claimed method. Moreover, it is unclear how the apparatus of Williams could be incorporated into a balloon or other catheter, as in the present invention. For example, Williams' description of the invention states:

> "In accordance with the invention herein, a treatment according to the invention comprises:
>
> "applying a photosensitizing agent to target tissue consisting essentially of tissues containing blood-carrying vessels supplying an undesired lesion, the photosensitizing agent being in a pharmaceutically acceptable composition for contact with said target tissue;
>
> "illuminating an area consisting essentially of the treated blood-carrying vessels with light from a laser emitting light of a frequency and energy which excites the photosensitizing agent and coagulates blood in said vessels." (col. 3, lines 20-41)

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[3] It is noted that Claim 34 was not elected in the election of January 3, 2005, and therefore is being canceled without prejudice or disclaimer.

The laser referenced in the above passage is a precisely scanned beam that must be directed to very specific areas of tissue (i.e., "blood-carrying vessels supplying an undesired lesion"), as evidenced by the following:

> "The present invention provides particular benefits from a higher degree of selectivity in the treated tissues. The spot size of the laser and duration of the exposure should be adjusted depending on the dimensions and location of the lesion vascular tissue or target vessel to contact not substantially more than the surface of discernible target vessels. Preferably, the spot size of the laser is within the range of about 25 microns to about 2000 microns with exposure times on the order of pico seconds up to one second." (col. 4, lines 1-9)

While Williams provides meager details regarding how such targeted tissue is to be identified and how the beam is to be steered, presumably these require some type of optical or electro-optical imaging apparatus coupled with some form of laser scanning apparatus to precisely steer this small beam of light to the identified target tissue. The necessary miniaturization required to fit such hardware into a catheter would undoubtably be quite complicated. Further, the Examiner has provided no evidence that the technology to make such a catheter existed at the time of the present invention. MPEP 2143.02 requires that for the prior art to be modified or combined as prima facie obvious, there must be a reasonable expectation of success which is determined at the time the invention was made. The Examiner has provided no evidence of such a reasonable expectation of success at the time of the invention. Further, regardless of the details of such a hypothetical apparatus, it is clear that Williams is teaching very selective illumination of a very small portion of tissue proximal to the apparatus.

In contrast to this cumbersome approach, Applicants claim and teach easier, more reliable, and more failure safe methods of treatment based on application of a substantially uniform field of light to an area of tissue to be treated, as exemplified by the following:

> "In general, the method of the present invention involves one or more of the following steps. Initially, disease is diagnosed.... Thereafter ... PDT agent is applied to the disease site .... After a brief accumulation period ... excess agent is purged or flushed from the disease site, and a *substantially uniform light field is applied to the disease site in order to activate the agent associated with the diseased tissue*." (page 11, lines 8-17, emphasis added)

Thus, rather than attempting to precisely direct the activating light to small regions of tissue, as per Williams, the methods of the claimed invention allow simple uniform illumination to be used, wherein targeting is achieved through a combination of photosensitizer properties (i.e., targeting and pharmacokinetic properties resulting from the method of application) and selection of wavelength of the applied light. This latter point is illustrated by the following from the present application:

> "For treatment of superficial diseased tissue, the wavelength of the light is preferably chosen so as to allow optical penetration into the diseased tissue but to minimize further optical penetration beyond the diseased tissue into underlying healthy tissue. For example, visible light in the spectral region between 400-600 nm may be used to afford shallow penetration depths on the order of several millimeters or less. Use of such light affords efficacy in agent activation in superficial diseased tissues while simultaneously minimizing potential for deleterious photosensitization of underlying tissue." (page 11, lines 18-24)

Accordingly, the methods underlying the respective teachings in Williams and the claimed methods of the present application are completely different, and the apparatus necessary to employ the respective teachings is necessarily completely different. Hence, one skilled in the art could not combine the teachings in Williams with known balloon catheter or other catheter apparatus to arrive at the claimed invention.

Accordingly, Claims 23-28, 34 and 82 are not disclosed or suggested by the cited references and patentable thereover. Therefore, it is respectfully requested that this rejection be withdrawn.

IV. Information Disclosure Statement

Applicants are submitting herewith an information disclosure statement (IDS). Applicants also submitted IDSs on May 12, 2005 and on September 16, 2005. It is respectfully requested that all of these IDSs be entered and considered prior to the issuance of any further action for this application.

V. Conclusion

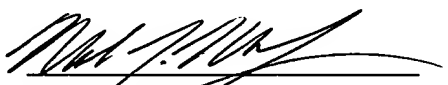
For at least the above-stated reasons it is respectfully submitted that the claims of the present application are in an allowable form and are patentable over the cited references. Accordingly, it is requested that the application be allowed.

If any fee should be due for this amendment, please charge our deposit account 50/1039.

Favorable reconsideration is earnestly solicited.

Respectfully submitted,

Date: October 20, 2005



Mark J. Murphy
Registration No. 34,225

COOK, ALEX, McFARRON, MANZO,
CUMMINGS & MEHLER, Ltd.
200 West Adams Street, Suite 2850
Chicago, Illinois 60606
(312) 236-8500

Customer No. 000026568